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# The Reality of ALS

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Norris, Katie, "The Reality of ALS" (2020). *Honors Projects*. 33.
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**The Reality of Battling ALS**

**Katie Norris**
**Dr. Van Hoomissen**

**Honors thesis**
**4/29/20**

**Into the Unknown**

Take a moment to imagine a scenario. You are healthy. You are active. You are able to pick up your children. You can put on your own clothes, brush your own teeth, and laugh when your spouse makes a joke. You have the normal minor aches and pains of getting old, but there is nothing that could stop you from simply living. However, those silly old aches and pains seem to turn into something more noticeable. Your muscles become weaker and you can no longer pick up the kids like you used to. You seem to lose your balance a lot more often. Overall, your body feels as if there is a weight dragging it down. Thinking it is simply part of aging, you go to your primary care physician to see if there is anything that could be done. Your physician confirms your worries, and talks to you about changing your diet and starting to exercise at a gym more regularly.

You follow your physician orders, yet, your symptoms get worse. You begin to slowly slur your words and you notice it starts to become difficult to wrap your fingers around your tooth brush and button your shirt. You panic. You type all of your symptoms into Google and scroll through numerous neurological disease: spinal muscular atrophy, progressive bulbar palsy, multiple sclerosis, progressive muscular atrophy, amyotrophic lateral sclerosis. Your heart stops. Amyotrophic Lateral Sclerosis. ALS. You read through the symptoms— stumbling, slurred speech, problems swallowing, muscle weakening/cramping, muscle stiffness— you know deep down that you have just found your diagnosis. Yet, this is impossible. How could you be one of 5,000 of the 330 million American that get diagnosis every year (Bromberg 2017). You take a big breath. You are over thinking. There are a million other explanation to what is currently happening. You make an appointment again with your physician, yet, this time she takes you more seriously. Your physician is at a loss of what it could be and refers you to a neurologist.

At the neurology appointment, your neurologist tells you it can be a number of diseases and that a series of test need to be done. You pipe up and confess that you have already played doctor on Google and you noticed many of your symptoms lined up with ALS. Your neurologist chuckles and reassures you that ALS is an extremely rare disease and tends to mimic other neurological diseases. You feel slightly relieved and begin to have hope again for a full recovery, however, you cannot shake the word ALS from your mind.

You start off by giving your neurologist a history of symptoms and going through an in depth physical examination. After, you begin the long list of testing to start narrowing down what exactly is happening to your body. A simple blood and urine test is done first and you are disappointed when everything comes back normal. Your physician continues with a nerve conduction study which measures the electrical activity of the nerves and muscle. You again become disappointed when muscle disease and peripheral nerve damage gets crossed off the list. As the testing continues, and the list gets shorter and shorter you begin to realize your worst fear is about to come true. You have ALS.

Your family does not take the news well, however, you are just grateful for a diagnosis. Even though you know there is no cure, you cannot yet face the fact that your entire life is about to change. At your first doctor's appointment, at the nearest ALS clinic, and your head spins as the neurologist, physical therapist, occupational therapist, respiratory therapist, nurses, dietitian, speech language pathologist, social worker, and mental health professionals cycle through; throwing an absurdly large amount of information at you. Yet, you are strong. You do your best to stay calm and taken in all the information, but the future of your new reality becomes real when greeted by the nurse from the palliative care team.

At first he asks general question about how you are coping with the diagnosis. However, as the conversation continues, he eases into two words that you are not quite familiar with: advance directive. He explains that it is a document that gives you the opportunity to be in charge of your future care when you can no longer communicate. You figure that you might as well get it out of the way now and agree to fill it out. As you begin to fill out the form you read the statement "I want to receive tube feeding", you freeze. Want? You do not want any of this. What you want is to live. You want to be able to pick up the kids. You want to be able to brush your own teeth. You want to able to tell the people in your life how much you truly love them. You want this nightmare to be over. You feel the warm salty tears run down your worn battered down face. They do not stop. That person who loves you dearly holds you so tight you can no longer breath. The reality of the upcoming years has hit you. You realize that you will spend your last days watching your body slowly deteriorate. Slowly losing the function of your limbs, voice, mouth, and your ability to breath, until you are trapped inside your own head. You will become your own prisoner— fully aware of what is happening, yet, have no control to stop any of it.

Along with this comes a wave of guilt. Your love ones did not sign up this financial and emotional burden. For a brief moment you think you should end it all. But when finally catch the eyes of your partner, you know that could never be an option. No matter what, you want to spend as much time as possible with the people you have built this incredible life. You are not going to give up that easy. You are going to find a way to still live.

**Neurons Rule our Bodies**

This is just one scenario. The truth is no one knows how they are going to react to a diagnosis like ALS. Yet, how ALS physically effects patients is the same. ALS is well known for the slow deterioration of a patient's body which eventfully leads to death. Many patients and families struggle to comprehend though of what exactly is happening to their bodies. When you google "what causes ALS", you get a variety of explanations ranging from motor neuron death to loss of function of upper and lower neurons. Essentially, Dr. Ragole from OHSU explains that the neurons in your spine and brain that causes muscles to contract and move, die off. This leads to loss of motor function which starting with the loss of skeletal muscle but eventually, patients lose their ability to eat, breath, talk, and swallow. Figure 1 below is from the ALS Association, which explain to families the functional difference between a healthy motor neuron and dead motor neuron effected by ALS. The neurons that die off ultimately causes the person to become

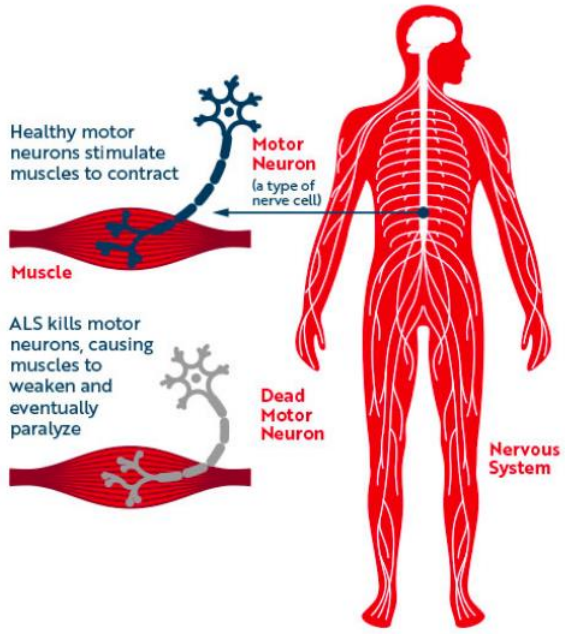


Figure 1. Difference between healthy motor neuron and ALS effected motor neuron (*What is ALS?* 2020)

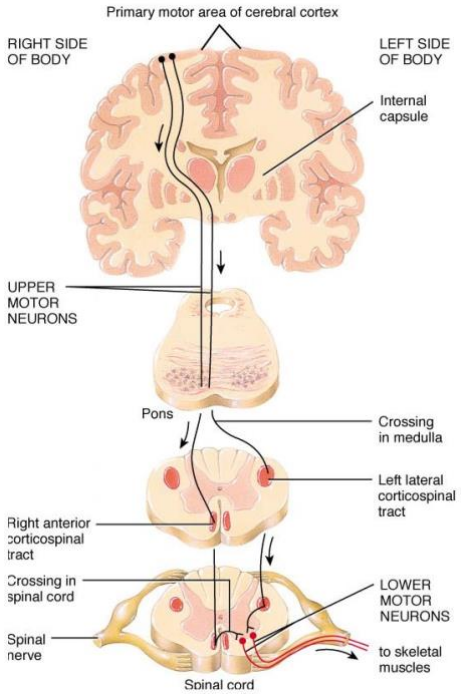


Figure 2. Location of upper and lower motor and how they connect (Kiernan 2011)

a quadriplegic and rely on ventilators and feeding tubes for survival. Furthermore, Dr. Ragole expresses that the distinguishing feature of ALS is how the disease effects both upper and lower motor neurons. ALS stands for "amyotrophic lateral sclerosis" which comes from the French language. Amyotrophic refers to the present of atrophy, or shrinkage, of muscle due to the loss of lower motor neurons. These are nerves that extend from the spinal cord to the muscles and lateral refers to the side of the spinal cord (Figure 2). Sclerosis, then refers the hardening from scar tissue due to the loss of upper motor neurons. The upper motor neurons extend their axons from the cerebral cortex through the lateral side of the spinal cord (Figure 2). It is through this defining aspect of the loss of both upper and lower motor neurons that doctors can confirm the diagnosis of ALS.

**Test, test, and Some More Test**

The characteristics of ALS were first noticed by a French neurologist named Jean-Martin Charcot in the mid-1800s and since then, they have helped doctors differentiate ALS from other motor neuron diseases. Primary lateral sclerosis (PLS) and progressive bulbar palsy (PBP), for example, are characterized by the loss of only upper neurons, while progressive muscular atrophy (PMA) is characterized by the loss of only lower motor neurons. However, ALS involves the loss of both upper and motor neurons which contributes to the severity of the disease. It is common though for patients to first develop one these other motor neuron diseases before developing ALS. Cassy Adams, a social worker for the ALS Association, expresses that the nonprofit also offers their services to patients with PLS, PBP, and PMA because of their similarities to ALS. Table 1, below, refers to the different signs and symptoms that occur due to the loss of upper and/or lower motor neurons. Neurologist have found that speech and slow

movements are associated with the degradation of upper motor neurons and muscle weakness and cramps are associated with degradation of lower motor neuron (Table 1).

Table 1. Symptoms found through patient's description and signs determined through neurologist Diagnostic Examination of upper and lower neuron function (Bromberg 2017)

| *Upper Motor Neuron Loss* | | *Lower Motor Neuron Loss* | |
|---|---|---|---|
| *Symptoms* | *Signs* | *Symptoms* | *Signs* |
| *Bulbar Region* | | *Bulbar Region* | |
| • Slurred speech | • Spastic speech | • Muscle shrinkage | • Muscle atrophy |
| • Difficulty swallowing | • Choking while drinking | • Weakness | • Muscle weakness upon testing |
| *Arms and Legs* | | *Arms and Legs* | |
| • Slow movements | • Slow development of strength | • Muscle twitches | • Fasciculations |
| • Unsteady walking | • Spastic gait | • Muscle cramps | • Cramps during muscle testing |
| | • Jumpy tendon reflexes | | • Characteristic findings on EMG study |

Since there is not a single laboratory test that can confirm ALS, Dr. Ragole explains that physicians rely on a pathological diagnosis, neurological examination, and electrodiagnostic test to confirm the disease. Additionally, many other neurological diseases that mimic ALS, which adds to the difficulty of diagnosis. Electrodiagnostic test consist of nerve conduction test and electromyography (EMG) test. The nerve conduction test "records responses form sensory and motor nerves by taping electrodes over nerves or muscles" which is similar to EKG recordings (Bromberg 2017). EMG, on the other hand, is the most accurate test in determining lower motor neuron loss and "a small needle electrode is inserted into various of muscles, which records the electrical activity generated in the muscles when the patient gently contracts the muscle

(Bromberg 2017). Other laboratory test such as blood and urine samples are also taken to rule out other diseases. Dr. Ragole expresses that when patients finally get the diagnosis they are generally relieved. He shares that "The majority of the time patients already have a feeling that they have ALS, so the diagnosis does not always come as a shock. In general, most are just grateful to have a diagnosis even if there is no cure".

As the disease progresses, however, more symptoms arise. About 40-50% of patients experience frontotemporal lobe dementia (FTLD) which is the second most common type of dementia, right after Alzheimer's (Bromberg 2017). FTLD is caused by a degeneration of nerve cells in the frontal and temporal section of the brain. This leads the patient to lose the ability to socially interact, become much more irritable and selfish, develop compulsive behaviors, and have a hard time making a decision (Lu et al. 2009). Patients do not lose their memory like Alzheimer's patients, however, instead, their personality changes drastically and in severe cases patients become unrecognizable to their friends and family. FTLS is diagnosis through clinical examination, a screening questionnaire, or a MIR, which determines if there is atrophy of the frontal lobe (Bromberg 2017). Furthermore, researchers do not know what is causing the degeneration of nerves in this part of the brain and FTLD has been known to develop in other neurological diseases like Parkinson's (Lu et al. 2009).

Another neurological symptom that develops in about 50% of ALS patients is the pseudobulbar affect (PBA), which is thought to be associated with the loss of upper motor neurons. PBA results in an uncountable impulse to laugh or cry and can be trigged by a sad or funny situation. In severe cases, it can interfere with the patient's ability to communicate. PBA can result in patients having a perpetual smile, which people have interpreted as ALS patients having a nice personality (Bromberg 2017). Doctors can easily diagnosis PBA through clinical

examination because of the uncontrollable laughter and cry. There are two medications called Amitriptyline—an antidepressant— and Nuedexta that can be used to treat PBA (Bromberg 2017). Other symptoms that can occur through the progression of ALS are fatigue, scaly skin, excessive sweating, eyes sting, biting of cheek, swelling of hands or feet, and muscles spasms. ALS does not cause any physical pain to the patient except for muscle cramps that can develop.

**Down the Rabbit Hole we Go**

Diagnosis is only the start for patient who battle ALS and, generally, the expected life span after diagnosis is two to five years. ALS is typically seen in adults between the ages of 40 and 70 years old and is 20% more common in males than in females (Wijesekera and Leigh 2009). ALS clinics and the ALS Association are two places where patients can find support and treatment. Here in Portland, there are ALS clinics at Providence and OHSU where patients sit through four hour long appointments every couple of months and are seen by a rotation of a neurologist, physical therapist, occupational therapist, respiratory therapist, nurses, dietitian, speech language pathologist, social worker, and mental health professionals. This is a way for patients to have all their needs met in one appointment and experience an overwhelming amount of support through the duration of their battle with ALS.

Rick Warren, a nurse who is part of the palliative care team at the Providence ALS clinic, explains that they are very realistic with patients from the beginning which can be difficult. Even though his main job involves end of life care, on the first or second visit, he says, the patient will be visited by someone from the palliative care team to discuss filling out an advance direct. An advance direct is a legal document that instructs health professions how a patient wants to be treated when they can no longer communicate. ALS results in patients losing their ability speak,

swallow, and breath, so when there only way of survival is through a feeding tube and ventilator, doctors need to know if this is the course of action the patient wants to take. Warren expresses that patients generally have a very hard time making these decisions early on because they are typically still independent and have not thought much about the future progression of the disease. However, he states that it is important to encourage patients to fill out this document before they lose their ability to communicate, because it allows them to still have some control of their future, in some aspect.

Another group that ALS patients will be contacted by after diagnosis is the ALS Association. The ALS association is a nonprofit that helps ALS patients and families nationwide. When a neurologist diagnoses a patient with ALS, they will notify the ALS Association so they can have a social work reach out to them. Adams expresses that, as a social worker, she is usually one of the first people that will meet with a patient after diagnosis. Generally, she says that they will offer to meet at the patient's home to discuss how they are processing the diagnosis and start talking about equipment they will need. Adams explains that about half of the time, patients are not quite ready to talk to a social worker, which is perfectly understandable. She states that they are there to help the patients with anything they need and at their own pace. The ALS Association helps provide patients obtain wheel chairs, shower chairs, chair lifts, etc. to try and make the transition as easy as possible. They also offer support groups for patients and host fundraises to spread awareness and raise money for families struggling to pay medical cost.

Adams explains that "One of the most frustrating parts of my job is dealing with the limitations of the health care and social services". Many patients have not reached the age where they qualify for Medicare, so they have a hard time getting insurance to cover the cost of necessary equipment. The ALS Association does their best in finding families used equipment if

they cannot afford it themselves or if their insurance does not cover it. Another reality families have to face is becoming full time caregivers. Insurance does not cover the cost of caregivers, so most patients rely on family members to help them carry out every day task like getting changed and taking a shower. Adams expresses that the ALS Association does their best to support the family too because they understand how this disease completely changes everyone's lives. Many patient's families have to the remodel their homes in order to accommodate for their lifestyle changes. Adam conveys that it is heartbreaking to witness so many families struggle with the financial aspect of ALS and it is an unnecessary stress that is added on top of everything else they are going through.

**Clueless**

The question arises though why is this happening? What is causing patients upper and lower neurons to die? Dr. Ragole simply puts as "We honestly do not know". To date there is no known cause of ALS or understanding of why patient's neurons are slowing degrading, however, we do know that there are two types. About 90% of patients are thought to have sporadic ALS (sALS) and about 5% to 10% of patients are thought to have familia ALS (fALS) (Bromberg 2017). fALS indicates that the disease is passed down genetically and the onset of symptoms usually present themselves a lot earlier in life. fALS is most commonly associated with a mutation in the superoxide dismutase 1 (SOD1) gene which makes up about 20% of all fALS cases (Mackenzie et al. 2007). However, over 17 genes have been associated with fALS and the mode of inheritance can either be autosomal dominant, autosomal recessive, or x-linked (Bromberg 2017). As for sALS there is even less know. There has been over 13 genes and loci that are associated with sALS, yet, no research has been able to determine the cause of mutation

to onset the disease (Mackenzie et al. 2007). Furthermore, researchers have not been able to uncover any environmental factors that could also lead to the neuronal death. There are though several theories that researchers have come up with to help understand what biological processes are killing motor neurons.

Glutamate is the neurotransmitter that activates upper and lower motor neurons, however, when the concentrations are too high in the synapses, it causes glutamate excitotoxicity. As you can see in Figure 3, the nerve/astrocyte relationship is vital because astrocytes are responsible for about 90% of glutamate reuptake (Mahmoud et al. 2019). When astrocytes are impaired, there is an increase of glutamate concentration in the synapses which is detrimental to nerve cell. The cause of astrocyte impairment is unknown, however, it has been found to result in a cascade of events, leading to neuronal death.

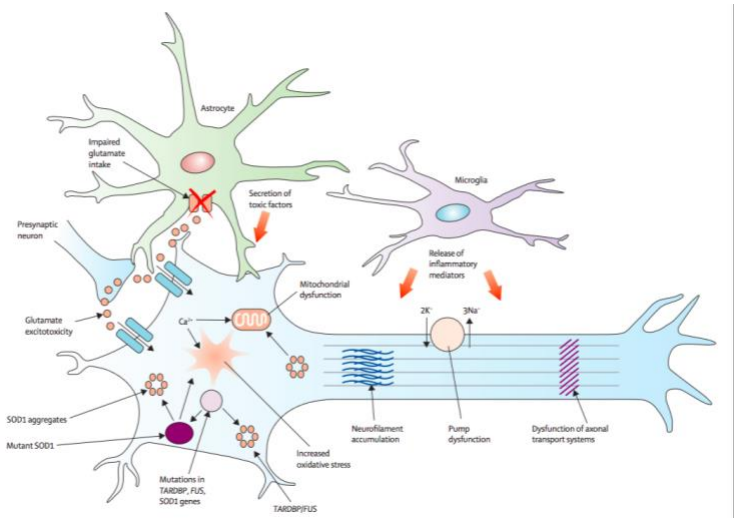


Figure 3. Location where possible neuronal death theories take place and how they interact with one another (Kiernan et al. 2011).

Excessive oxidative stress has appeared to occur in ALS patients which is easily induced with glutamate excitotoxicity. Short-term oxidative stress is a natural process that happens in cells and refers to the presents of free radical oxygen species (ROS). ROSs are produced when

oxygen is reduced in the mitochondria and released along the electron transport chain or form as necessary intermediates in enzyme reactions (Phaniendra et al. 2014). Furthermore, ROSs can help repair damage to cells or detoxify reactive intermediates. Long-term or excessive oxidative stress though can cause damage to the mitochondria of the neuron cells (Figure 3.). The mitochondria is the power house of the cell, and if it becomes dysfunctional, then the cell will die. Another factor that can contribute to an increase in oxidative stress are mutated genes (Figure 3). For example, the SOD1 gene is responsible for producing the copper-zinc superoxide dismutase molecule which converts ROD into harmless water molecules (Eisen et al. 2008). So in many fALS cases, when the SOD1 gene is mutated, it prevents this processes from happening, causing mitochondrial dysfunction and eventually, neuronal death.

Mutated genes also contribute to the accumulation of protein aggregation (Figure 3). When a gene does not provide the right code for the structure of a protein, it causes a protein to be misfolded. Misfolded proteins cause great dysfunction to the neuron cells because they begin to stick to one another creating aggregates. When protein aggregation occurs, the neuron cell is unable to break down the proteins, causing them to pile up and become toxic. Research has shown that a mutation in the SOD1 gene also leads to protein aggregation which contributes to neuronal death (Eisen et al. 2008). Lastly, the role of the immune system is to remove dead cells, however, in ALS patients, the excessive oxidative stress and protein aggregation causes the immune system to become overactive, contributing to the neuronal damage (Figure 3).

**So What if it Kills Me**

Like many terminally ill patients, ALS patients have a hard time accepting that there is no cure for their disease. Some turn to clinical trials for answers, however, only a select minority

can participate. Clinical trials have a strict criteria related to the progression of the disease, age of patient, and the severity of symptoms, for example. With ALS clinical trials, Dr. Ragole explains, it is important that the patient is in early stages of the disease. From a research point of view, this makes sense, because they want to understand how the drug effects degradation of motor neuron. They also do not always know the side effects of the drug, so they want to put as few patients as possible in harm's way. Yet, from a patient's perspective it is simply frustrating. In recent years, there has been much back lash from terminally ill patients on the restriction on non-FDA approve treatments. Many do not understand why they cannot just try an experimental treatment if they give full consent. To them, they are going to die regardless, so what harm is there in trying an experimental drug.

In May 2018, the Trump administration finally heard the frustrations of the people and passed the Right to Try Act or the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act. This act allows terminally patients to try any non-FDA approved drugs that are still under experimental studies. The only restriction is that is must have past phase one of the clinical trial study (Office of the Commissioner 2020). However, there is a catch. Dr. Ragole express he has had patients often ask about the Right to Try act, yet, what many do not realize is that they have to pay for the treatment. Typically, experimental drugs cost hundreds of thousands of dollars, but when you participate in a clinical trial, those fees are waived. The Right to Try Act may have given patients the accesses to the newest experimental drugs, however, it does not cover the cost. Dr. Ragole frustratingly admits that the Right to Try Act is for the top 1% because no insurance is going to be willing to pay for a non-FDA approve drug. Furthermore, no average patient is going to be able to afford it on top of all other expenses. The Right to Try Act was used though by an ALS patient to get into the most successful ALS

clinical trial called Brainstorm. 34-year-old navy veteran Matthew Bellina, who was one of the advocates for the Right to Try Act, used Brainstorm's experimental treatment without meeting the criteria for the clinical trial. It would have cost Bellina over $300,000, however, the CEO of Brainstorm covered the cost for him because of his passion and help getting the Right to Try Act to pass (Court 2018).

Brainstorm is a type of stem-cell therapy that targets the regeneration of new neuronal cells through autologous MSC-NTF therapy (Admin 2019). Doctors extract some of a patient's bone marrow and place it in a culture to produce mesenchymal stem cells (MSC). MSCs are multipotent stem cells that can differentiate into many different types of cells. The MCS are harvest and differentiated to secreted high levels of neurotrophic factors (NTF) (Admin 2019). NTFs help support the growth of neurons and there are no genetic modifications done to the cells. The MSC-NTF cells are then injected into the patient to promote neuronal growth in areas of the brain and spinal cord where there is the greatest neuronal damage (Admin 2019). Brainstorm has seen some success in their research and are currently entering into phase 3 of their clinical trial (Admin 2019).

Another clinical trial that has had some recent success that was brought my attention by Dr. Ragole, is a project called Centaur. Centaur developed a drug called Amylyx 0035 which goal is to slow down the progression of ALS, by preventing neuronal death and degeneration. Amylyx 0035 boost the metabolism and protein synthesis through a method called heat shock protein to help fold protein to their proper shape (Campos 2019). Essentially, this will help prevent protein aggregation and slow down neuronal death. Currently, Centaur just past animal trial phase and there has been no human testing done yet. There has also been no data published to confirm that the drug work, however, Dr. Ragole states that the head researcher on the team is

one of his colleagues, and she has given him verbal confirmation that Amylyx has been successful. Even though researchers are still struggling to find the cure for ALS, Dr. Ragole expresses that "For the first time in the past 100 years our technology is catching up with our ideas. In the next five to ten years, I really do feel like we are going to see some significant breakthroughs in many areas of neurological research".

**Connecting with Depression**

Warren stated that one of the hardest aspects to witness is seeing people struggle to accept the disease and how a lack of communication with friends and families prevent this acceptance. Many ALS patients struggle with depression and anxiety and the psychological stress brought on by the disease is overwhelming. Studies have found that it can associated with a faster mortality rate due to the fact that anxiety appears to develop closer to end of life and patient suffering from depression are more likely to deny end of life care (Kurt et al. 2007). A study done by the National Institute of Health found that out of their 131 participants, over a third were are on antidepressants (Atassi et al. 2010). Yet, only 6% reported to have severe depression (Atassi et al. 2010). Furthermore, they reflected that severe depression was less common in their study in comparison to the general population. Even though depression is prevalent in the ALS community, it should be stressed that patient's mental state in no way impact their physical symptoms, so it should not affect any patient's participation in clinical trials (Atassi et al. 2010).

Lauren Brown, a nurse from the Providence ALS clinic, expresses that she frequently treats patients who show signs of depression which presents challenges in connecting with them. She explains that this causes all of her relationships with her patients to be very unique. For

example, she once had very depressed young man who was giving her a hard time in doing his breathing exercises. Instead of getting frustrated, she knelt down on one knee, so they could be eye level, and she simply talked to him as a friend and not a patient. He responded by flipping her off. At first she was taken back, however, she quickly realized that this was his way of expressing "I love you". She chuckled and stated that "You have the ability to be able to connect with every patient. The challenge is finding a language you both can speak". From then on, whenever she saw the young man, he would flip her off and she would do it right back.

**Mind Over Body**

Even though depression is prevalent throughout the ALS community, it does not appear that rates of depression drastically increases with diagnosis (Kurt et al. 2007). Adams expressed that in her experience, she is always surprised by the grace patients exhibit and many have similar perspectives to famous baseball player Lou Gehrig.

Gehrig brought national and international attention to ALS for the first time in 1939 in his "Luckiest man on the face of the earth" retirement speech. The "iron man" of baseball was diagnosis with disease which ended his career. However, his acceptance of ALS inspired millions of people and he revealed during his retirement speech that he had been "given a bad break but have an awful lot to live for" (Si 2009). Adams said this attitude is seen in many ASL patients. She shared a story of a middle age man who was recently diagnosed and he expressed to her that "he sees the disease as an opportunity to become his best self". Warren and Brown also both shared similar experience of patients using their diagnosis to travel or taking up different religious practices like Buddhism, which focuses on framing your mind into looking at something as positive. Even though ALS is a death sentence, it does not mean the patient has to

stop living. It is entirely up to the patient on how they handle the reality of the disease and through Brown's eyes she sees it as "the most beautiful awful disease ever". It is a battle that defines the human person which calls upon the patient to make the decision to acknowledge, love, and support their diagnosis of ALS.

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